PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
23725 PC 1		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK00/00425	27/07/2000	27/07/1999
International Patent Classification (IPC) or national classification and IPC A61K38/00		
Applicant HEMEBIOTECH A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 25 sheets.

CORRECTED VERSION

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27/02/2001	12.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fayos, C Telephone No. +49 89 2399 2180

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK00/00425

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-7,10-102,104-111, 113-118,121-125, 128,132-138	as originally filed			
8,9,103,112,119, 120,126,127, 129-131	as received on	13/10/2001	with letter of	10/10/2001

Claims, No.:

1-11	as received on	13/10/2001	with letter of	10/10/2001

Drawings, sheets:

1/49-37/49	as originally filed			
38/49-49/49	as received on	13/10/2001	with letter of	10/10/2001

Sequence listing part of the description, pages:

1-11, filed with the letter of 19.09.01

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☒ contained in the international application in written form.
   - ☒ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
see separate sheet

6. Additional observations, if necessary:
see separate sheet

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 6 and 9.

because:

☒ the said international application, or the said claims Nos. 6 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 9 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5, 7-8 and 10-11
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-5, 7-8 and 10-11
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-5, 7-8 and 10-11
	No:	Claims	-

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item I

Basis of the report

1- An amended set of claims has been enclosed to the applicant's letter dated 10.10.01. However, the mentioned set of claims wherein the amendments are indicated was not enclosed in said letter.

1.1- Claims 1-**53** have been deleted.

1.2- New claim **9** has been introduced to the rhPBGD produced by the method of any of claims **2-6**.

1.3- In claim 2 b), a reference to the introduction of the production strain according to claim **1** has been added.

1.4- New claim 6 is based on old claim 44. However, it does not meet the requirements of Article 34(2)(b) PCT (see item III 3- below).

Re Item II

Priority

2- The priority date (27.07.1999) appears to be valid for the subject matter claimed. Hence, D4 is not prior art in this case. D4 cited in the international search report will probably become relevant in the European phase.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

3- The amendments filed with the letter dated 10.10.01 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT.

The amendment concerned is that of claim 6.

No basis could be found in the application as originally filed for "a method for the preparation of rhPBGD" wherein the PBGD "is recombinant human PBGD based on any of Seq. ID NO 3 (clone PBGD 1.1) and Seq. ID NO 4 (non-erythro PBGD 1.1.1).

2.1- Claims 1-5 and 7-11 meet the requirements of Article 34(2)(b) PCT.

2.2- The corrections made to the description of the present application and the drawings do not contravene Article 34(2)(b) PCT.

The applicant's observations (10.10.01) submitted with the amended claims have been considered.

5- Claim 9 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined.

Claim 9 attempts to define the subject-matter in terms of the result to be achieved (i. e. "able to lower the levels of PBG and ALA in mice during an acute attack of porphyria in a transgenic mouse model where the PBGD gene has partially been knocked-out") which merely amounts to a statement of the underlying problem "a rhPBGD which is able to lower the levels of PBG and ALA in mice during an acute attack of porphyria in a transgenic mouse model where the PBGD gene has partially been knocked-out" . The technical features necessary for achieving this result are missing. Therefore, no opinion on novelty, inventive step and industrial applicability will be formulated with regards to the subject matter of claim 9.

5.1- A rhPBGD produced by the method of any of claims 2-6 could be considered as being novel over the prior art cited in the search report.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

6- Reference is made to the following documents:

D1: GROSS U ET AL: 'Haem precursors and porphobilinogen deaminase in erythrocytes and lymphocytes of patients with acute intermittent porphyria' CELLULAR AND MOLECULAR BIOLOGY,US,TARRYTOWN, NY, vol. 43, no. 1, 1 February 1997 (1997-02-01), pages 29-35, XP002082339 ISSN: 0145-5680

D2: SASSA S: 'Diagnosis and therapy of acute intermittent porphyria' BLOOD REVIEWS,GB,EDINBURGH, vol. 10, no. 1, 1 March 1996 (1996-03-01), pages 53-58, XP002082340

D3: GRANDCHAMP B: 'Acute intermittent porphyria' SEMINARS IN LIVER DISEASE,DE,STUTTGART, vol. 18, no. 1, 1 January 1998 (1998-01-01), pages 17-24, XP002082341

D4: see item VI

6.1- Additional document:

D5: MOLECULAR CELL BIOLOGY (Third edition- 1995) p 299-300

NOVELTY - Art. 33 (1) and (2) PCT

7- Claims 1-5, 7-8 and 10-11 appear to be novel in the light of the prior art cited in the search report:

7.1- The novel features are:

- a production strain of rhPBGD as in claim 1,
- a method for the preparation of rhPBGD as in claims 2-5,
- an expression plasmid as in claim 7,
- a DNA fragment as in claim 8, and
- a rhPBGD as in claim 10 or claim 11.

INVENTIVE STEP - Art. 33 (1) and (3) PCT

8- Claims 1-5, 7-8 and 10-11 appear to be inventive over the cited prior art for the reasons stated below:

8.1- The claims have been reformulated to define the problem to be solved to be to provide a production strain and methods of preparing rhPBGD by use of said production strain in order to produce sufficient quantities of enzyme, i. e. functional recombinant human PBGD, to make enzyme replacement therapy possible.

The objective problem posed in the present application is to provide means for large scale production of rhPBGD.

The solution proposed is to provide a production strain as in claim 1 of the present application.

8.2- The prior art documents cited in the search report, alone or combined, fail to describe a large scale production of rhPBGD.

In fact, the present application provides a production strain which is particularly suitable for large-scale production of the enzyme since it has been engineered not to express the endogenous Phrophobillinogen Deaminase of E. coli. In order to provide this production strain, it was necessary to clone a functional enzyme selected from a large group of PBGD variants. In view of the large number of mutations and polymorphisms, it was not straightforward which one to select and whether it would be suitable for the purpose.

Thus, in real world context, it would not have been obvious for the skilled man to provide a production strain as in claim 1 of the present application.

Hence, claims 1-5, 7-8 and 10-11 can be considered as being inventive.

It is well known (see any of D1-D3) that AIP is an autosomal dominant disorder resulting from a patrial porphobilinogen deaminase (PBGD) deficiency. Furthermore, the gene coding for PBGD has been identified, its cDNA has been cloned and the mutations which cause AIP are also known (see D2 and D3).

It would therefore be obvious for the skilled man, to compensate the deficiency in PBGD in a subject by administrating PBGD (directly, or by means of gene therapy) and hence normalize the levels of PBGD in said subject.

However, there is no suggestion in any of the prior art documents, taken alone or in combination to provide a production strain as in claim 1 of the present application.

INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT

9- Claims 1-5, 7-8 and 10-11 appear to be industrially applicable.

Re Item VI

Certain documents cited

10- Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 99 37325	29.07.1999	27.01.1999	27.01.1998 30.12.1998